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(54) Pharmaceutical or cosmetic formulations containing coumarins and proanthocyanidins

(57) The present invention relates to the use of coumarins such as esculoside, esculetin, extracts containing them and mixtures thereof, in combination with dimeric and oligomeric proanthocyanidins, in topical formulations for the treatment of peripheral vasculopathies, including the complications of acute venous stasis, or of the unesthetisms related to capillary alterations, or to improve the cicatrization processes. These coumarins, alone or in combination with proanthocyanidins, are also useful in atopical dermatitis and in the treatment of the haematomas.

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Description

The present invention relates to the use of novel formulations for the topical use containing combinations of coumarins, such as esculoside, esculetin, extracts containing them or mixtures thereof, with dimeric and oligomeric proanthocyanidins for the treatment of peripheral vasculopathies related to an impaired peripheral microcirculation; moreover, the invention relates to the use of said coumarin derivatives in combination with proanthocyanidins in the cicatrization processes and in the complications of chronic venous stasis (leg heaviness, ulcus cruris) and in the treatment of internal and external hemorrhoids. In a strictly cosmetic field, the combinations are used in the treatment of unesthetisms related to superficial capillaries (couperose), rosacea, telangiectasias and the like. It has surprisingly been found that a strong synergism exists between these coumarin derivatives and proanthocyanidins.

The microvasculokinetic activity of esculoside, responsible for many of the properties of the combinations (cicatrizing and antihemorrhoid) was evaluated by non-invasive techniques such as infrared photopulsoplethysmography, Laser-Doppler and video-capillaroscopy which allows to check the districtual microangiotectonic and the capillary morphological changes before and after the treatment with the tested substances. Esculoside induces favourable changes in the capillary density, up to 300% higher than the basal values.

In the combinations according to the invention, the weight ratio of coumarin derivatives to proanthocyanidins preferably ranges from 4:1 to 1:4. For example, combinations of three parts of esculoside and one part of proanthocyanidins (selected from proanthocyanidin A2 and the procyanidole oligomers of a different origin, preferably those extracted from Vitis vinifera or Camellia sinensis) exert synergistic activities which are qualitatively different from those of the single components; a non-limiting interpretation of this fact is that esculoside increases the proanthocyanidin absorption at the topical level as a consequence of the increase in districtual blood flow, and therefore of water. Particularly synergistic is the modulating activity on the cicatrization process, wherein a stimulation of the tissue restoration and a regular orientation alongside the cicatricial axis are observed, thus preventing the formation of keloids.

Analogously, these combinations are favourably used in the unesthetisms and on the reduction of the couperose. In the latter case, 20 individuals of both sexes were treated on one side of the face in the temporal-zygomatic area with a 1.5% esculoside and 0.5% of proanthocyanidin A2 formulation and on the other side with placebo. The treatment continued for 60 days twice a day; the evaluation of the intensity of the unesthetism was performed by means of scores and with objective evaluations measuring the colour intensity of the area treated with the combination of the invention compared with that treated with placebo. After the treatment, a 41% reduction in the unesthetism was observed, using the patient himself as control.

Particularly important is the healing effect of the combinations according to the invention, which effect can be used in plastic surgery as well as in decubitus and venous stasis ulcers. To evaluate the cicatrization effect, patients were selected which had undergone superficial surgery, having wounds of a size suitable to the simultaneous treatment with the combination of the invention and with placebo. For example: cauterized wounds larger than 2 cm, so as to allow, after suturation, the treatment of 1 cm with a placebo formulation and of 1 cm with a formulation containing 1.5% esculoside and 1.5% procyanidole oligomers from Vitis vinifera. Immediately after the treatment, the adhesion edges and nearby areas of the wound were checked with a videocapillaroscope (Scopeman-Moritex Video Imaging System, Alpha Strumenti, Milan), fitted with a halogen-light optical probe with 50 to 400 x magnifications, measuring the capillary density (number of blood-perfused capillaries per area unit) and evaluating the space orientation of the capillaries and their morphology. 15 Minutes after the treatment, the capillary density increased by 100% compared with the basal one and with the placebo-treated control. Surprisingly it has been found, and it is a part of the present invention, that following the improved districtual circulation (the cicatricial area is usually poorly vascularized, contrary to what was believed up to now) and the fibroblast proliferation stimulation, a remarkable induction of a regular capillarogenesis takes place. The wound healing with the products of the present invention turned out to be accelerated and at the same time modulated. In bedsores and torpid ulcers, the larger blood flow to the necrotic area leads to a restoration of the tissue healing properties and a reduction and disappearance of the ulcer. Analogous results are obtained in the hemorrhoidal pathology, in which the simultaneous effect on arteries and veins allows a fast regression of venous stasis.

The treatment above described relates to the treatment of cauterized wounds and or healing wounds, or of cutaneous ulcers, or of venous stasis conditions. Further, it has surprisingly been found that the administration of a formulation containing 1% esculetin and 0.3% procyanidanole oligomers from Camellia sinensis on newly formed scars leads to a faster disappearance of the cicatritial outcome, with a remarkable reduction in the hyperhaemic area compared with the controls. The result of such a treatment is particularly important in the exposed body areas, where facial esthetic surgery, removal of naevi and the like are performed.

Moreover, it has been found that the above cited coumarins, alone or in combination with proanthocyanidins, are markedly effective in the treatment of atopic dermatitis and haematomas of any origin. Therefore, topical administrations of a formulation containing 2% esculetin on atopic dermatitis induce a reduction of the dermatitis within one week or in even shorter times, depending on the severity and degree of the pathology. The same formulation, applied on haematomas, made them to disappear within a few days, probably thanks to the microvasculokinetic activity of the product.

Particularly useful as excipients for the formulations of the invention proved to be phospholipids, pure or in form of the natural mixtures thereof, which allow a quick absorption of the substances themselves, even though other excipients can advantageously carry the products of the invention, enhancing their therapeutical or dermocosmetic functionalities.

The formulations according to the invention contain, besides the above defined active principles, carriers, additives, preservatives and the like known in pharmaceutical technique, such as those listed in the examples reported hereinbelow, which illustrate the invention without limiting its scope.

Example I - Gel containing esculoside and procyanidole oligomers from Vitis vinifera. 100 g of gel contain:

Esculoside	1.50 g
96% Procyanidole oligomers	1.50 g
Hydrogenated castor oil 40(OE) (Cremophor RH40 - BASF)	1.00 g
Propylene glycol	1.50 g
Preservatives	0.10 g
Hydroxyethyl cellulose (Natrosol 250 HHX - Aqualon)	3.00 g
Purified water	q.b. a 100 g

Example II - Alcoholic fluid gel containing esculoside and proanthocyanidin A2. 100 g of gel contain:

Esculoside	1.50 g
Proanthocyanidin A2	0.50 g
Hydrogenated castor oil 40(OE) (Cremophor RH40 - BASF)	5.00 g
Propylene glycol	3.00 g
Carbomer 940 (Carbopol 980 - Goodrich)	1.00 g
Ethanol 95°	45.00 g
Phosphatidylcholine (Phospholipon 90- Natterman)	1.60 g
Glyceryl 6(OE) Caprilate/Caprinate (Softigen 767)	15.00 g
Preservatives	0.40 g
Butylhydroxytoluene	0.05 g
α-Tocopherol	0.20 g
Ascorbic acid	0.30 g
Dimethicone copolyol (SF 1188 - General Electric)	2.00 g
10% Triethanolamine	5.00 g
Purified water	q.s. to 100 g

Example III - Cream containing esculoside and proanthocyanidin A2.
100 g of cream contain:

Esculoside	2.50 g
Proanthocyanidin A2	
Hydrogenated castor oil 40(OE)	1.00 g
(Cremophor RH40 - BASF)	2.00 g
Propylene glycol	2.00 g
Carbomer 934 (Carbopol 934 P - Goodrich)	0.50 g
Alkyl C_{10-30}-Acrylate (Carbopol 1382 - Goodrich)	0.50 g
Ethanol 95°	15.00 g
Preservatives	0.40 g
Cetyl Palmitate (Cutina CP - Henkel)	8.00 g
Polyisoprene (Syntesqual - Vevy)	5.00 g
Polysorbate 80 (Tween 80 - ICI Americans)	2.00 g
α-Tocopherol	0.20 g
Ascorbyl palmitate	0.10 g
Hydrogenated lanolin (Lanocerina - Esperis)	5.00 g
Dimethicone 350 cps (Tegiloxan 350 - Tego)	0.50 g
Phosphatidylcholine (Phospholipon 90- Natterman)	2.50 g
10% NaOH sol.	2.40 g
Purified water	q.s. to 100 g

Example IV - Gelified emulsion containing esculetin and procyanidanole oligomers from Camellia sinensis. 100 g of emulsion contain:

Esculetin	1.00 g
96% Procyanidole oligomers	0.30 g
Isopropyl myristate	5.00 g
Preservatives	0.40 g
Perfume	0.10 g
Polyacrylamide, C_{13-14}-isoparaffin and lauric alcohol 7(OE) (Sepigel 305 - Seppic)	3.00 g
Purified water	q.s. to 100 g

Example V - Gelified emulsion containing esculetin. 100 g of gelified emulsion contain:

Esculetin	2.00 g
Isopropyl myristate	5.00 g
Preservatives	0.40 g
Perfume	0.10 g
Polyacrylamide, C_{13-14}-isoparaffin and lauric alcohol 7(OE) (Sepigel 305 - Seppic)	3.00 g
Purified water	q.s. to 100 g

Claims

1. Pharmaceutical and/or cosmetic formulations for the topical use, containing as active principles:

   a) coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, combined with
   b) dimeric and oligomeric proanthocyanidins.

2. Pharmaceutical and/or cosmetic formulations according to claim 1, characterized in that the contained proanthocyanidins are selected from the group consisting of proanthocyanidin A2, procyanidole oligomers extracted from Vitis vinifera and Camellia sinensis, and mixtures thereof.

3. Pharmaceutical and/or cosmetic formulations according to claim 2, characterized in that the contained proanthocyanidin is proanthocyanidin A2.

4. Pharmaceutical and/or cosmetic formulations according to claims 1-3, for the treatment of peripheral vasculopathies connected with impairments of the arterial or venous circles and of unesthetisms related to impaired capillary permeability and fragility, particularly for the treatment of superficial or deep scars; internal and external hemorrhoids; conditions related to chronic venous stasis, such as stasis ulcers and telangiectasias; couperose and peripheral capillaropathies.

5. Pharmaceutical and/or cosmetic formulations for the topical use, containing as active principles coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, optionally combined with proanthocyanidins, for the treatment of atopic dermatitis and haematomas of any origin.

6. Pharmaceutical and/or cosmetic formulations according to any one of the above claims, characterized in that they contain pure phospholipids or mixtures thereof as excipients.

7. The use of coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, combined with dimeric and oligomeric proanthocyanidins, for the manufacturing of a medicament for the topical use, intended for the treatment of peripheral vasculopathies connected with impairments of the arterial or venous circles and of unesthetisms related to impaired capillary permeability and fragility; superficial or deep scars; internal and external hemorrhoids; conditions related to chronic venous stasis, stasis ulcers and telangiectasias; couperose and peripheral capillaropathies.

8. The use of coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, optionally combined with dimeric and oligomeric proanthocyanidins, for the manufacturing of a medicament for the topical use intended for the treatment of atopic dermatitis and haematomas of any origin.

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EUROPEAN SEARCH REPORT

Application Number
EP 95 11 1054

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	PHLEBOLOGIE (GERMANY), 1994, 23/3 (71-77), GERMANY, HOSTETTMANN K. ET AL 'ZU INHALTSSTOFFEN UND PHARMAKOLOGIE PFLANZICHER VENENMITTEL' * page 72, column 1, paragraph 3 - page 73, column 3, paragraph 2 *	1-8	A61K35/78 A61K31/37 A61K31/35 A61K31/765
A	EP-A-0 348 781 (TECNOFARMACI SPA ;INDENA SPA (IT)) 3 January 1990 * claims 1-3,12 *	1-8	
A	EP-A-0 275 224 (INDENA SPA ;SANOFI SA (FR)) 20 July 1988 * the whole document *	1-8	
A	EP-A-0 412 300 (INVERNI DELLA BEFFA SPA) 13 February 1991 * page 3, column 1, line 25-31 *	1-8	
A	GB-A-1 589 294 (INVERNI DELLA BEFFA SPA) 13 May 1981 * claims *	1-8	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	6 November 1995	Leherte, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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